Anti-metastatic potential of resveratrol and its metabolites by the inhibition of epithelial-mesenchymal transition migration, and invasion of malignant cancer cells

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Highlights

- Resveratrol has chemopreventive and chemotherapeutic potentials on cancer metastasis.
- Resveratrol may reverse the EMT-induced morphological changes.
- Therapeutic effects of resveratrol were shown on cancer metastasis in various cancer models.
- Anti-metastatic effects appeared in the metabolites or analogs of resveratrol.

Review

Anti-metastatic potential of resveratrol and its metabolites by the inhibition of epithelial-mesenchymal transition migration, and invasion of malignant cancer cells

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Abstract

BACKGROUD : Increased epithelial-mesenchymal transition (EMT) and cell migration and invasion abilities of cancer cells play important roles in the metastatic process of cancer. Resveratrol is a stilbenoid, a type of natural polyphenol found in the skin of grapes, berries, and peanuts. A number of experiments have examined resveratrol's ability to target diverse pathways associated with carcinogenesis and cancer progression.

PURPOSE : This article aims to present updated overview of the knowledge that resveratrol and its metabolites or analogs have the potential to inhibit metastasis of cancer via affecting many signaling pathways related with EMT, cancer migration, and invasion in diverse organs of the body.

CHAPTERS : This article starts with a short introduction describing diverse beneficial effects of resveratrol including cancer prevention and the aim of the present study. To address the effects of resveratrol on cancer metastasis, mechanisms of EMT, migration, and invasion and their relevance with cancer metastasis, anti-metastatic effects of resveratrol through EMT-related signaling pathways and inhibitory effects of resveratrol on migration and invasion are highlighted. In addition, anti-metastatic potential of resveratrol metabolites and analogs is addressed.

CONCLUSION : Resveratrol was demonstrated to turn back the EMT process induced by diverse signaling pathways in several cellular and animal cancer models. In addition, resveratrol can exert chemopreventive efficacies on migration and invasion of cancer cells by inhibiting the related pathways and target molecules. Although these findings display the anti-metastatic potential of resveratrol, more patient-oriented clinical studies demonstrating the marked efficacies of resveratrol in humans are still needed.

Keywords: Resveratrol; Resveratrol metabolites; Epithelial-mesenchymal transition; Cancer metastasis

Abbreviations

EMT : Epithelial-mesenchymal transition (EMT)
TGF : transforming growth factor
ECM : extracellular matrix
MET : Mesenchymal-epithelial transition
EGF : epidermal growth factor
MMP : matrix metalloproteinases
CRC : colorectal cancer
RPE : retinal pigment epithelial
TCF/LEF : T-cell factor/lymphoid enhancer factor
LPS : lipopolysaccharide
VEGF : vascular endothelial growth factor
FGF : fibroblast growth factor
ERK 1/2 : extracellular signal-regulated kinase 1/2
Gli1 : glioma-associated oncogene homolog 1
ROS : reactive oxygen species
HGF : hepatocyte growth factor
LLC : Lewis lung carcinoma
HUVECs : human umbilical vein endothelial cells
VCAM-1 : vascular adhesion molecule 1
HSE : hepatic sinusoidal endothelium
SPARC : Secreted Protein Acidic and Rich in Cysteine
TPA : 12-O-tetradecanoylphorbol-13-acetate
JNK : c-Jun N-terminal kinase
HRG-β1 : heregulin-β1
HER-2 : human epidermal growth factor receptor 2
MTA1 : metastasis associated 1
DHS : 4,4′-dihydroxy-trans-stilbene
HPIMBD : 4-(E)-[(4-hydroxyphenylimino)-methylbenzene,1,2-diol]
miR : microRNA
Ago2 : Argonaute2

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Introduction

Cancer prevention or treatment by natural dietary agents has drawn attention worldwide due to their ingenious chemopreventive ability (Bishayee, 2009). Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a natural polyphenololic compound belonging to stilbene phytoalexin, which is the stilbene' sub-group of non-flavonoid phenolic compounds (Bastin and Djouadi, 2016, Lee et al., 2016, Waterhouse, 2002). Resveratrol exists in various vegetables such as berries, grapes, peanuts, and red wine (Athar et al., 2007, Carter et al., 2014). Particularly, red wine has been believed to be the main source resveratrol in the human, but recent study discovered that peanut sprout contains abundant bioactive resveratrol by accumulating it through germination (Yu et al., 2016). Certain plants may also produce resveratrol to fend off pathogenic attacks, thereby having it serve as an antimicrobial agent (Brittany Wolfe, 2015).

The extensive studies over the past decades have shown that resveratrol has potential to chemopreventive and chemotherapeutic effects. Moreover, recent studies discovered that resveratrol has been shown to appear many biological activities related to cancer prevention and treatment by regulating cell division and growth of cancer cells, apoptosis, angiogenesis, and metastasis (Athar et al., 2007, Ndiaye et al., 2011, Saiko et al., 2008). These studies have demonstrated a strong chemopreventive effect of resveratrol in diverse organs undergoing cancer progression such as skin, breast, prostate, lung, pancreas, and ovary (Fremont, 2000, Kang et al., 2012, Kopp, 1998, Roldan et al., 2003, Shankar et al., 2011, Yi et al., 2011).

In addition, these chemopreventive actions of resveratrol have been extensively studied at the molecular and cellular levels, such as cellular signaling, enzymatic pathways, p53-mediated apoptosis (Kroon et al., 2010, Lin et al., 2002, Shih et al., 2004). Nevertheless, the

biological activity of resveratrol may be limited by poor absorption and first-pass metabolism, and these limitations lead to low bioavailability (Cottart et al., 2010, Kapetanovic et al., 2011, Walle et al., 2004). Whereas resveratrol is metabolized into sulfated and glucuronidated forms within 15 min of entering the bloodstream, its metabolites, which may be the active principle, circulate in serum for up to 9 h (Saiko et al., 2008). For this reason, some researchers have studied inhibitory effects of resveratrol metabolites or its analog on cancer progression and metastasis (Savio et al., 2016). For instance, a study has revealed anti-cancer effects of resveratrol metabolite on highly metastatic colon cancer cells (Aires et al., 2013). Dias et al. also showed that two resveratrol analogs (trimethoxy-resveratrol and piceatannol), displayed the higher bioavailability and chemopreventive effects, which is reduced tumor volume, and decreased tumor growth in the xenografts, in LNCaP-Luc-xenograft model (Dias et al., 2013).

Up to date, anti-tumor mechanisms and pathways of resveratrol have been extensively reviewed in different cancers (Athar et al., 2007, Carter et al., 2014, Smoliga et al., 2011). In the present review, we will highlight the current understanding of the inhibitory role of resveratrol in cancer metastasis developed through fundamental steps such as epithelial mesenchymal transition (EMT), migration, and invasion processes (Kim et al., 2015). Furthermore, we will also focus on the anti-metastatic effect of metabolites and analogs of resveratrol.

1. Effects of resveratrol on cancer metastasis via regulation of EMT

1.1 EMT and its relevance with cancer metastasis

Epithelial cells normally interact each other via cell-cell adhesion and are bound by a basal lamina at their basal surface. EMT is an critical process through epithelial cells lose their cell-cell interaction and gain mesenchymal phenotype, leading to enhanced migratory capacity, invasiveness, elevated resistance to apoptosis, greatly increased production of extracellular matrix (ECM) components, and rearrangement of cytoskeletons (Jeon et al., 2016, Kalluri and Weinberg, 2009, Son and Moon, 2010). EMT constitutes recognized mechanisms for regulating developmental processes in embryos (Kong et al., 2011), forming mesenchymal cells in injured tissues, and initiating the invasive and metastatic behavior of epithelial cancer (Kalluri and Weinberg, 2009).

The principal difference between normal development and pathological processes such as cancer metastasis is that normal cellular and molecular events follow highly regulated spatial and temporal plans during development, whereas during pathological transformation the order of events may be stochastic and time-independent, or particular events may be bypassed (Larue and Bellacosa, 2005). During tumorigenesis, malignant transformation may be associated with signaling pathways promoting EMT, and EMT may increase the motility and invasiveness of cancer cells and initiate cancer metastasis (Chaffer and Weinberg, 2011, Thiery et al., 2009).

Mesenchymal-epithelial transition (MET), the reverse process of EMT, is also critical for normal development of many tissues and organs, numerous embryonic events, and metastasis of carcinomas (Thiery et al., 2009). Cancer cells in primary tumor lose epithelial properties by E-cadherin repression and penetrate through the basement membrane with increased invasive properties. As an epithelial marker, E-cadherin is expressed in epithelial tissues and mediates cell-cell interactions, and therefore, loss of E-cadherin function has been

implicated in cancer progression and metastasis (Beavon, 2000). These cells enter into the bloodstream through intravasation, and then when the cells circulating bloodstream exit the blood vessel, they undergo MET for anchoring at the metastasis site (Chaffer and Weinberg, 2011). This type of cancer is well known as secondary tumor, which means spreading of the primary tumor to other sites and is responsible for 90% of mortalities linked to cancer (Xue and Hemmings, 2013). Therefore, EMT and MET are thought to play a fundamental role during the early steps of invasion and metastasis of carcinoma cells (Boyer et al., 2000).

E-cadherin expression in epithelial tumors can be negatively regulated by a number of zinc finger-family transcription factors, including Snail, Slug, Twist, E12, SIP1 (ZEB2) and δEF1 (ZEB1), each of which has been reported to bind to the E-cadherin promoter to repress its transcription (Bolos et al., 2003, Castro Alves et al., 2007, Conacci-Sorrell et al., 2003, Grooteclaes and Frisch, 2000, Hajra et al., 2002, Huber et al., 2005, Rosivatz et al., 2002, van Grunsven et al., 2003). Snail and ZEB proteins directly bind to E-cadherin promoter to repress its transcription, whereas Twist represses E-cadherin indirectly (Peinado et al., 2007, Yang and Weinberg, 2008). And also the downregulation of E-cadherin is balanced by the increased expression of mesenchymal neural cadherin (N-cadherin), which results in a ‘cadherin switch’ that alters cell adhesion (Wheelock et al., 2008, Yilmaz and Christofori, 2009). The switch usually refers to EMT and is closely associated carcinoma and metastasis (H Rai, 2014, Pyo et al., 2007). The cells undergoing EMT also express high levels of fibronectin and vimentin. Fibronectin is a glycoprotein of ECM that binds to membrane-spanning receptor protein called integrins (Pankov and Yamada, 2002). It plays important roles in cell adhesion and induces EMT (Pankov and Yamada, 2002, Park and Schwarzbauer, 2014). During EMT, epithelial cell adhesion switches from cell-cell contacts to mainly cell-

ECM interactions to raise the possibility that fibronectin may have a role in promoting this transition (Park and Schwarzbauer, 2014). Lately, a study suggested that vimentin, a type III intermediate filament protein that is expressed in mesenchymal cells, mediated the reorganization of cytoskeletons to maintain the mechanical integrity in cancer cells undergoing EMT (Liu et al., 2015, McDonald, 1989). The intermediate filament composition changes with the repression of cytokeratin and the activation of vimentin expression (Huang et al., 2012) and the changes in intermediate filament composition may enable cell motility, possibly owing to the interaction of vimentin with motor proteins (Mendez et al., 2010).

In addition, several signaling pathways have been known to be associated with the EMT process. TGF-β, Wnt, and Notch signaling pathways are the key signaling pathways which induce EMT pathways, and they regulate the activation of EMT-inducing transcription factors above-mentioned. In recent studies within 5 years, Hedgehog and epidermal growth factor (EGF) signaling pathways also have appeared as the new mechanisms mediating the EMT process on early cancer metastasis (Gao et al., 2015, Li et al., 2016, Vergara et al., 2011). Recently, microRNAs (miRs) that are 22-nucleotide non-coding RNAs and suppress their targets through mRNA destabilization and translational inhibition have been emerged as crucial regulators of EMT and MET, targeting multiple components involved in these processes (Lamouille et al., 2013). These signaling pathways inducing EMT and miRs in cancer metastasis could be effective targets of many chemopreventive agents such as resveratrol and other polyphenols to exert their anti-metastatic potential.

1.2 Anti-metastatic effects of resveratrol through EMT-related signaling pathways and miRs

Many studies showed that resveratrol would suppress the progression of tumor invasion and metastasis by inhibiting EMT-associated signaling pathways (Xu et al., 2015). TGF-β is a well-known cytokine that promotes proliferation, invasion, angiogenesis, immunosuppression, and EMT of cancer cells, and TGF-β/Smads signaling pathway has been known to activate EMT in cancer metastasis (Blobe et al., 2000, Heldin et al., 2012). TGF-β signaling is transferred from cell membrane to nucleus through Smad proteins (Heldin et al., 1997), which are intracellular proteins that transduce extracellular signals of TGF-β ligands to the nucleus (Whitman, 1998) thorough TGF-β type 2 and type 1 serine/threonine kinase receptor, respectively (Akiyoshi et al., 1999, Feng and Derynck, 2005, Heldin et al., 1997, Massague and Chen, 2000). As a result, the signaling pathway of TGF-β increased repression of E-cadherin and the activation of N-cadherin and matrix metalloproteinases (MMP) expression, consequentially leading to the EMT process (Grande et al., 2002, Uttamsingh et al., 2008).

Resveratrol was revealed to turn back the cell morphological changes from a classical mesenchymal phenotype to an epithelial phenotype that is induced by TGF-β (Blobe et al., 2000, Li et al., 2013). In A549 lung cancer cells, resveratrol (20 μM) inhibited TGF-β-induced EMT by increasing expression of E-cadherin and decreasing the expression of fibronectin and vimentin as well as EMT-inducing transcription factors Snail and Slug (Wang et al., 2013). Qing Ji et al. demonstrated that resveratrol (12 μM) inhibited TGF-β-induced EMT and the invasion and metastasis of colorectal cancer (CRC) by inhibiting Smad2/3 in CRC (Ji et al., 2015). In retinal pigment epithelial (RPE) cells, EMT is also a critical step in the pathogenesis of proliferative vitreoretinopathy. Keijiro et al. found that resveratrol (50 μM) induces MET and inhibits TGF-β2-induced EMT of RPE cells by deacetylating SMAD4 (Ishikawa et al., 2015).

The Wnt signaling pathway has been implicated in EMT during embryonic development and cancer progression (Huber et al., 2005, Larue and Bellacosa, 2005, Xu et al., 2009). When the Wnt signaling pathway is activated, cytoplasmic β-catenin is accumulated in the nucleus, where it associates with the T-cell factor/lymphoid enhancer factor (TCF/LEF; a coactivator β-catenin) and promotes the expression of target genes involved in EMT (Brantjes et al., 2002, Son and Moon, 2010). Numerous studies also indicate that the activation of Wnt/β-catenin signaling can promote transcriptional changes in order to drive EMT in cancer (Anastas and Moon, 2013). In MCF7 breast cancer cells, expression of WNT1, which is a proto-oncogene protein Wnt-1, was sufficient to induce EMT-like changes, including upregulation of Snail and downregulation of E-cadherin expression (Anastas and Moon, 2013, Chance et al., 1999, McMahon and Moon, 1989). Some studies have documented that the Wnt signaling pathway cross-talks with the TGF-β and PI3K/Akt signaling pathways in EMT process (Son and Moon, 2010); for example, a complex with a LEF formed by Smad2 and Smad4 causes repression of E-cadherin gene, and Smad4 and LEF induce mesenchymal phenotypes such as upregulation of fibronectin and vimentin, and the acquisition of migratory ability (Nawshad et al., 2007). Anti-tumor effect of resveratrol on CRC was demonstrated by inhibition of Wnt/β-catenin signaling, which is activated in over 85% of sporadic colon cancers (Robbins and Itzkowitz, 2002, Son and Moon, 2010). In LoVo and HCT116 CRC derived cells, resveratrol (50 μM) inhibited Wnt/β-catenin signaling, leading to the downregulation of Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1), which plays an important role in CRC matastasis (Ji et al., 2013). It was also found that low concentration of resveratrol (10 μM) significantly inhibited Wnt signaling in colon-derived

cells (HT29 and RKO cells) due in part to regulation of intracellular β-catenin localization. (Hope et al., 2008).

The transcription factor NF-κB also can promote EMT as well as cancer migration and invasion (Huber et al., 2004, Maier et al., 2010). NF-κB is a protein complex that controls transcription of DNA, cytokine production, and cell survival, and linked to cancer progression (Albensi and Mattson, 2000, Gilmore, 2006). Several studies demonstrated that NF-κB is an important regulator of EMT in different cell types (Chua et al., 2007, Huber et al., 2004, Maier et al., 2010, Min et al., 2008, Shin et al., 2006). The roles for NF-κB were found to be associated with the expressions of EMT-related genes such as E-cadherin, snail and ZEB1, MMP-7, MMP-9 and MMP-13 (Barbera et al., 2004, Bloomston et al., 2002, Chua et al., 2007, Maier et al., 2010). NF-κB can be activated by PI3K/Akt signaling activation to promote EMT and metastasis of cancer cells. In Panc-1 pancreatic cancer cells, resveratrol (50 μM) suppressed metastatic potential in vitro by modulating EMT-related factors (E-cadherin, N-cadherin, vimentin, MMP-2, and MMP-9) via the PI-3K/Akt/NF-κB signaling pathway (Li et al., 2013). In mouse melanoma model, resveratrol (16 μg/ml) inhibited tumor migration and EMT by the downregulation of NF-κB activity, which was induced by lipopolysaccharide (LPS) (Chen et al., 2012).

The specific signaling pathways that triggering EMT also include EGF, vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF) signalings (Thiery et al., 2009, Vergara et al., 2010). As results of these signaling, the events such as disruption of E-cadherin mediated cell-cell interaction due to the activation of several transcriptional repressors, Snail, Slug, Twist, and ZEB were induced, and thereby the EMT process was simulated (Vergara et al., 2011). In MCF-7 breast cancer cells, a combined treatment of EGF

(100 ng/ml) and resveratrol (25 μM) reversed the altered cell morphology and motility and overexpression of EMT markers induced by EGF-induced EMT (Vergara et al., 2011). This study revealed that EGF induced EMT via extracellular signal-regulated kinase 1/2 (ERK 1/2) signaling pathway and that resveratrol was able to repress EGF-induced ERK activation, providing new evidence of inhibitory effect of resveratrol on EGF-mediated caner progression (Vergara et al., 2011).

Recent studies have suggested that Hedgehog family ligands regulate the EMT process (Bailey et al., 2007, Huber et al., 2005) and that Hedgehog signaling pathway affects many types of cancer undergoing EMT process, for example gastric, hepatoma, lung, pancreatic, and prostate cancer (Ahmad et al., 2013, Chen et al., 2011, Karhadkar et al., 2004, Lei et al., 2013, Li et al., 2012, Yoo et al., 2011). Hedgehog signaling is essential for normal embryonic development and plays critical roles in adult tissue maintenance, renewal and regeneration, control tissue construction and remodeling by regulating the viability and migratory activity of various types of Hedgehog-responsive progenitor cells (Beachy et al., 2004, Omenetti and Diehl, 2008, Sicklick et al., 2006, Watkins et al., 2003). Hedgehog signaling also could be a crucial regulator of metastasis (Velcheti, 2007) because activation of the Hedgehog pathway leads to an increase in Snail protein expression and a decrease in E-cadherin and tight junctions (Li et al., 2006).

The recent finding indicated that LPS exposure resulted in an increase in cell motility, along with an upregulation of the transcription factor glioma-associated oncogene homolog 1 (Gli1), which is a transcription factor in the Hedgehog signaling pathway (Traiffort et al., 2010). However, treatment with resveratrol (10 and 20 μM) inhibited LPS-induced morphological changes, decreased the expression of LPS-induced markers of EMT

and inhibited the expression of Gli1, resulting in the inhibition of in vitro cell motility and invasiveness, suggesting that resveratrol may suppress the EMT process by inhibiting the Hedgehog signaling pathway partially (Li et al., 2014). The anti-metastatic effects of resveratrol through the inhibition of the Hedgehog signaling were also founded in gastric cancer (Gao et al., 2015), pancreatic cancer (Li et al., 2016), and osteosarcoma (Sun et al., 2015).

Recently, it was found that miRs can regulate the EMT process by targeting EMT transcription factors such as ZEB1/2 and Snail/Slug and epithelial and mesenchymal markers including E-cadherin, N-cadherin, and vimentin. The miR-200 family including miR-200a, miR-200b, miR-200c, miR-141, and miR-429 maintain the epithelial phenotype in such a way that they enhance the repression of ZEB levels (Abba et al., 2016). Snail is repressed by several microRNAs, including miR-29b and miR-30a (Lamouille et al., 2013), and Slug is targeted by its unique set of regulating miRs such as miR-506, miR-124, and miR-181a (He et al., 2013, Roy-Chaudhuri et al., 2014, Yang et al., 2013). Besides the regulation on the transcription factors, miR-9 directly targets E-cadherin, thus promoting EMT and the mesenchymal phenotypes of mammary epithelial cells (Ma et al., 2010). Conversely, miRs such as miR-194 and miR-138 reduce mesenchymal markers such as N-cadherin and vimentin, respectively, thereby inhibiting EMT and the metastasis (Meng et al., 2010, Zhang et al., 2016). Moreover, diverse miRs are implicated in the EMT process by affecting the cellular architectural components necessary for tight junction, cell-cell adhesion, and epithelial junction (Lamouille et al., 2013).

Meanwhile, not much is known about how resveratrol specifically affects the EMT process in cancer models by mediating miRs regulation. A previous report revealed that

suppression of tumor metastasis was mediated by resveratrol in lung cancer in *in vitro* (10 μM of resveratrol) and *in vivo* (20 mg/kg of resveratrol) models. In this study, resveratrol was found to inhibit the miRNA-520h-mediated signaling cascade that alters EMT-related signal molecules such as Akt, NF-κB, and FOXC2 (Yu et al., 2013). Also in breast cancer, resveratrol (25 μM and 50 μM) caused reversal of EMT by upregulating miR200c expression and altering ZEB1 and E-cadherin expression as well as induced expression of miR-141 that resulted in a significant suppression of invasiveness (Hagiwara et al., 2012).

2. Effects of resveratrol on cancer migration and invasion

2.1 Mechanisms of migration and invasion in cancer metastasis

Metastasis is a complex, multi-step process by which primary tumor cells invade adjacent tissue, enter the systemic circulation, translocate through the vasculature, arrest in distant capillaries, extravasate into the surrounding tissue parenchyma, and finally proliferate from microscopic growths (micrometastasis; the spread of a cancer from its original location to other sites in the body) into macroscopic secondary tumors (Fidler, 2003).

As aforementioned, metastasis of cancer begins with EMT, and then the cancerous cells can gain the migratory and invasive ability to enter the bloodstream through intravasation. Generally, cancer cells have a broad spectrum of migration and invasion strategies : they can migrate individually or collectively as multicellular groups (Friedl and Wolf, 2003). First, the single-cell migration involves five molecular steps that change the cell shape, its position, and the tissue structure through which it migrates (Friedl and Wolf, 2009). Second, collectively migrating cells form two major zones such as a proteolytic microtrack zone generated by leader cells, and the macrotrack zone that is formed by subsequent cells

widening this microtrack. These multi-cellular groups retain cell-cell adhesions while single cells loose the interactions (Friedl and Alexander, 2011, Friedl and Wolf, 2003).

Signaling pathways that control cytoskeletal dynamics in tumor cells and the turnover of cell-matrix and cell-cell junctions play important roles in cancer cell migration into the adjacent tissues (Chambers et al., 2002, Friedl and Alexander, 2011, Friedl and Wolf, 2003, Sahai, 2007).

Next, proteolytic enzymes are closely associated with tumor invasion. MMPs are calcium-dependent zinc-containing endopeptidases, and belong to a larger family of proteases known as the metzincin superfamily (Verma and Hansch, 2007). MMPs also have important functions in pathologic conditions that are characterized by the excessive degradation of ECM, such as tumor metastasis (Westermarck and Kahari, 1999, Yoon et al., 2003). MMPs were initially thought to facilitate tumor cell metastasis by destroying the basement membrane and other components of ECM, because MMPs has ECM-degrading activity, and the high levels of their activity and increased tumor metastasis were correlated (Yoon et al., 2003). Therefore, they are considered key enzymes for tumor invasion and metastasis (Liabakk et al., 1996). Among these, MMP-2 and MMP-9 are thought to be more important in metastasis (Snoek-van Beurden and Von den Hoff, 2005). Therefore, cancer metastasis is progressed by a series of these processes such as EMT, migration and invasion through the main factors that regulate them.

2.2 Inhibitory effects of migration and invasion of resveratrol on cancer

In many studies for cancer metastasis, resveratrol has been shown the potential to inhibitory effect on cancer migration and invasion in diverse *in vitro* and *in vivo* studies. In

hepatoma cell line of AH109A, resveratrol suppressed the reactive oxygen species (ROS)-potentiated cell invasion due to expression of hepatocyte growth factor (HGF), a known cell motility factor (Miura et al., 2004). The authors explained that the reason for this chemopreventive effect is that exogenously added ROS promoted the intracellular peroxide level and the expression of HGF, and the following treatment of resveratrol or its metabolite(s) inhibited the HGF expression through ROS scavenging action. This anti-oxidative property of resveratrol was also exerted in *in vivo* rat models (Miura et al., 2004). Mirura et al. also demonstrated that resveratrol dose-dependently suppressed solid tumor growth and metastasis by dietary feeding 10 or 50 ppm resveratrol to Donryu rats subcutaneously implanted with an ascites hepatoma cell line of AH109A (Miura et al., 2003).

The treatment of resveratrol (2.5 and 10 mg/kg) also found to significantly reduce the metastatic potential (56%) in mice bearing highly metastatic Lewis lung carcinomas (LLCs) as well as tumor volume and tumor weight, through the inhibition of DNA synthesis and LLC-induced neovascularization and tube formation (angiogenesis) of human umbilical vein endothelial cells (HUVECs), indicating that resveratrol also showed anti-tumor and anti-metastatic activities in lung carcinoma (Kimura and Okuda, 2001).

Oral administration of trans-resveratrol (20 mg/kg/twice per day) decreased hepatic metastatic invasion of B16M melanoma cells inoculated intrasplenically. The mechanism of this anti-metastatic effect involves a trans-resveratrol (1 μM)-induced inhibition of vascular adhesion molecule 1 (VCAM-1) expression in the hepatic sinusoidal endothelium and decreased B16M cell adhesion to the endothelium via very late activation antigen 4 (Asensi et al., 2002). Salado et al. also identified anti-metastatic effects of oral dose of resveratrol (1 mg/kg) on hepatic metastasis of B16M cells caused in large part by the p

roduction of pro-inflammatory cytokines (interleukin-18) (Salado et al., 2011).

A study showed that resveratrol decreased MMP-2 mRNA and protein levels as well as Secreted Protein Acidic and Rich in Cysteine (SPARC) gene and its protein expression in a brain tumor model, indicating that resveratrol may affect the two major factors in the ECM remodeling occurring with brain tumor invasion (Gagliano et al., 2005). In an oral cancer model, resveratrol suppressed the migration ability of SCC-9 cells stimulated by 12-O-tetradecanoylphorbol-13-acetate (TPA), known as a potent tumor promoter, through a reduction of gelatinolytic activity, secretion, and expression of MMP-9 at the transcriptional and translational levels. Specifically, resveratrol (25~100 μM) inhibited the phosphorylation of c-Jun N-terminal kinase (JNK)1/2 and ERK 1/2 involved in downregulating the protein expression and the transcription of MMP-9, demonstrating an anti-metastatic potential of resveratrol against oral cancer (Lin et al., 2015, zur Hausen et al., 1979). Additionally, resveratrol exerted its anti-invasive effect in breast cancer. Resveratrol (10 μM) significantly inhibited heregulin-β1 (HRG-β1)-mediated MMP-9 expression in human MCF-7 breast cancer cells, and it significantly suppressed HRG-β1-mediated phosphorylation of ERK1/2 and invasion of breast cancer cells (Tang et al., 2008).

The treatment of resveratrol (0.2 mg/kg per day) delayed spontaneous mammary tumor development and diminished metastatic capacity in human epidermal growth factor receptor 2 (HER-2)/*neu* overexpressing transgenic mice, which developed multiple mammary tumors at an early age. Its anti-tumor and chemopreventive effect might be relevant to the downregulation of HER-2/*neu*, a proto-oncogene, expression in tumor cells (Provinciali et al., 2005).

In Panc-1 pancreatic cancer cells, resveratrol (50 μM) repressed cancer cell migration and invasion through the inhibition of the PI3K/Akt/NF-κB signaling pathway. In this study, resveratrol inhibited cell proliferation, migration, and invasion in a dose-dependent manner (Li et al., 2013).

In addition, some studies suggested that resveratrol may inhibit cancer progression by reducing the expression of various cancer metastasis-associated miRs. Resveratrol (25 μM and 50 μM) suppressed prostate tumor growth and metastasis through inhibition of miR-21 and pAkt, and elevation of PDCD4, which is negatively regulated by miR-21 (Sheth et al., 2012). In human SW480 colon cancer, protective effects of resveratrol appeared by manipulating the level of miR-663 and may help to potentiate the anti-metastatic effects (Tili et al., 2010). In addition, resveratrol suppressed colorectal cancer by specifically activating miR-34c, which is a candidate of tumor suppressing gene and epigenetically silenced in colorectal cancer, through upregulation of p53 (Yang et al., 2015).

3. Anti-metastatic potential of metabolites and analogs resveratrol

Recent studies revealed that preventive effects of resveratrol are very controversial since pharmacokinetic studies showed a low bioavailability and rapid clearance of resveratrol from the circulation (Athar et al., 2007, Delmas and Lin, 2011, Gescher and Steward, 2003). These low circulating levels could be explained by a rapid phase II metabolism that generates glucuronide and sulfate conjugates and five distinct metabolites of resveratrol that are found in the urine (Boocock et al., 2007, Wenzel et al., 2005, Wenzel and Somoza, 2005).

However, anti-tumor and anti-metastatic potentials of resveratrol metabolites and analogs have been receiving renewed attention. A study suggested that biological effects of

resveratrol could be mediated by its metabolites such as resvetratrol-3-O-sulfate, resveratrol-3-O-glucuronide, and resveratrol-4'-O-glucuronide, even the mixture induced a synergistic effect on inhibitory effect of cancer progression in SW620 human metastatic colon cancer cells mediated by ataxia telangiectasia-Rad3-related and cell cycle related genes such as p53 and p21 (Aires et al., 2013).

Additionally, as dietary agent, pterostilbene which is a natural potent analog of resveratrol showed the potential applications in prostate cancer management. The pharmacological inhibition of metastasis associated 1 (MTA1) which is associated with aggressive human prostate cancer by pterostilbene resulted in decreased proliferation and angiogenesis and increased apoptosis. Moreover, loss-of-function studies using human prostate cancer cells indicated direct involvement of MTA1 in inducing inflammation and EMT markers such as increase of vimentin and decrease of E-cadherin (Dhar et al., 2016). In addition, pterostilbene (50 μM) revealed anti-cancer activity by inducing tumor-suppressive miRs and Argonaute2 (Ago2) expression in breast cancer cells (Hagiwara et al., 2012). Ago2 is a central RNA interference (RNAi) component which represses breast cancer stem-like cell characteristics by upregulating tumor-suppressive miRs such as miR-16, miR-141, miR-143, and miR-200c (Hagiwara et al., 2012). Also, it showed cytotoxic effect on diverse cancer cells *in vitro* (Rimando et al., 2002). When orally ingested, pterostilbene is known to have 95% bioavailibility when resveratrol has only 20% bioavailibility. Moreover, it was more powerful in chemoprevention of colon cancer than resveratrol (Chiou et al., 2011). Therefore, pterostilbene is considered as a key analog of resveratrol that has several important advantages over resveratrol (Hagiwara et al., 2012).

Monica et al. also investigated the preventive effects of resveratrol analogue 4,4′-dihydroxy-trans-stilbene (DHS) on lung cancer metastasis. In this study, DHS (0.1~1 μM) induced a marked inhibition of LLC cell migration and matrigel invasion as well as significantly inhibited the metastasis in murine lung cancer model and zebrafish tumor model, suggesting that DHS could potentially be developed as a novel therapeutic agent for treatment of cancer and metastasis (Savio et al., 2016). An attempt to improve the efficacy of resveratrol, due to the poor efficacy of resveratrol on clinical use, had synthesized an analog, 4-(E)-[(4-hydroxyphenylimino)-methylbenzene,1,2-diol](HPIMBD), which has better anti-cancer properties than resveratrol (Savio et al., 2016). In other study, HPIMBD also decreased the metastatic properties of breast cancer cells by inhibition of EMT and downregulation of wnt/β catenin pathway (Anwesha Chatterjee, 2015).

As another analog of resveratrol, piceatannol that closely resembles resveratrol in structure (Potter et al., 2002) also exhibits anti-cancer activity by inhibiting spread of diverse cancer cells such as lymphoma, leukemia, prostate cancer, and colon cancer (Piotrowska et al., 2012). Piceatannol was identified to suppress both the proliferation and invasion of AH109A hepatoma cells via induction of cell cycle arrest at 25~50 μM and apoptosis at 100 μM and anti-oxidation, respectively (Kita et al., 2012). Recent studies displayed that piceatannol suppressed the invasion of prostate at 40 μM and breast cancer cells at 5 and 10 μM by inhibiting MMP-9 (Jayasooriya et al., 2013, Ko et al., 2012).

Conclusion

Currently, cancer is treated by diverse therapeutic tools such as surgery, radiotherapy, chemotherapy, hormonal therapy, immunotherapy, and targeted therapies (Palumbo et al.,

2013). However, the genetic heterogeniety of cancer evades these treatment pathways and continuously deters clinical efforts (Block et al., 2015). To overcome the limitations and provide more effective cancer treatment, the Halifax Project which was recently operated by a large international researcher group summarized potential targets related to cancer hallmarks and proposed the development of low-toxicity broad-spectrum therapies that can collectively impact important mechanisms and pathways for the genesis and spread of cancer (Block et al., 2015). Consequently, phytochemicals included in the integrative medicine, which uses diet and lifestyle therapies, were suggested as corresponding low-toxicity therapeutic approaches (Block et al., 2015). Within this environment, interest and research in chemopreventive activities of phytochemicals on cancer have been continuously growing.

Cancer cells use multiple survival signaling pathways to prevail over normal cells such as EMT and metastasis-related pathways (Bishayee, 2009). On the contrary, the polyphenols such as resveratrol may repress these signaling pathways occurring in cancer cells, leading to an effective cancer prevention and treatment.

EMT is a key process that initiates cancer metastasis by forming mesenchymal cell morphology that can permit cell migration. Thus, it is important to inhibit the EMT process in early cancer metastasis. However, resveratrol was demonstrated to turn back the EMT-related morphological changes induced by TGF-β, TGF-β/Smads, NF-κB, PI3K/Akt, EGF, and Hedgehog signaling pathways in several cellular and animal cancer models. Resveratrol can also exert chemopreventive efficacies on migration and invasion of cancer by inhibiting the related pathways or molecules such as MMPs, HGF (liver), HER-2/neu and VCAM-1 as shown in **Figure 1**. The previous studies showing the modes of actions of resveratrol was summarized in **Table 1**. The therapeutic effects of resveratrol on cancer metastasis have been

displayed in various organs such as breast, liver, lung, and skin. The treatment of this agent may enable to inhibit several phases of cancer metastasis: EMT, migration, and invasion.

Moreover, these anti-metastatic effects also appeared in the metabolites or analogs of resveratrol. DHS, a resveratrol analog, inhibited lung cancer metastasis, and HPIMBD decreases the metastatic properties of breast cancer cells by inhibition of EMT. Pterostilbene which is a natural potent analog of resveratrol showed the inhibitory potential in human prostate cancer cells. Synergetic effect on inhibitory effect in metastatic colon cancer can be also anticipated by metabolites of resveratrol such as RSV-3-O-sulfate, RSV-3-O-glucuronide, and RSV-4'-O-glucuronide. Taken together, the evidence reviewed in this article suggests that resveratrol and its metabolites or analogs have the potential to inhibit metastasis of cancer via affecting many signaling pathways in diverse organs of the body. Their effects were mainly observed in *in vitro* cellular and *in vivo* animal experiments in the range of their multiple dosages such as 0.1~100 μM and 0.2~20 mg/kg, respectively.

However, there are several limitations based on efficacy of resveratrol yet. More patient-oriented clinical studies demonstrating the marked efficacies of resveratrol in humans are still needed, and the scales of clinical experiments to ensure a statistical significance have to be secured. Moreover, there is also a need to consider the synergistic anti-cancer effect through co-treatment with resveratrol and other polyphenols to maximize the therapeutic potentials of natural compounds.

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Conflict of interest statement

None of the authors have any conflicts of interest to declare.

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Figure Legend

Figure 1. ***Anti-metastatic potentials of resveratrol through the inhibition of EMT, migration, and invasion of cancer cells***. During tumorigenesis, malignant transformation may be associated with signaling pathways promoting EMT, and EMT may increase the motility and invasiveness of cancer cells and initiate cancer metastasis. The cells undergoing EMT can dissolve the basement membrane with increased invasive properties regulated by MMPs. Later, the cells enter the bloodstream through intravasation, and exit the bloodstream through extravasation, they undergo MET for anchoring at metastatic sites. However, resveratrol turns back the EMT-related morphological changes induced by TGF-β, TGF-β/Smads, NF-κB, PI3K/Akt, EGF and Hedgehog signaling pathways as well as by modulation of miRs. Moreover, it can suppress the migratory and invasive properties of the cells entering metastasis phase by regulating MMPs, HGF (liver), HER-2/neu, VCAM-1, and miRs. Resveratrol can also exert chemopreventive efficacies on migration and invasion of cancer by inhibiting the related pathways.

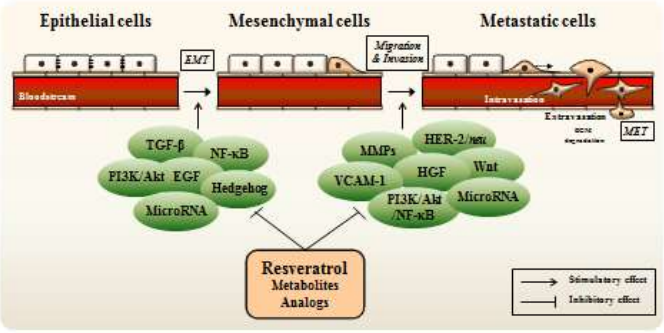

Table 1. Target signalings or molecules of resveratrol (or metabolites and analogs) representing inhibitory effect on cancer metastasis

Agents	Metastasis stages	Target signaling or molecules	References
Resveratrol	EMT	TGF-β	(Li et al., 2013), (Wang et al., 2013), (Ji et al., 2015), (Ishikawa et al., 2015)
		NF-κB	(Li et al., 2013), (Chen et al., 2012)
		EGF	(Vergara et al., 2011)
		Hedgehog	(Gao et al., 2015), (Li et al., 2016), (Traiffort et al., 2010), (Li et al., 2014), (Sun et al., 2015)
		MicroRNA	(Yu et al., 2013), (Hagiwara et al., 2012)
	Migration/ Invasion	HGF	(Miura et al., 2004)
		VEGF	(Kimura and Okuda, 2001)
		VCAM-1	(Asensi et al., 2002)
		IL-18	(Salado et al., 2011)
		MMPs	(Gagliano et al., 2005), (Tang et al., 2008)
		Wnt	(Hope et al., 2008)
		HER-2/*neu*	(Provinciali et al., 2005)
		PI3K/Akt /NF-κB	(Li et al., 2013)
		MicroRNA	(Sheth et al., 2012), (Tili et al., 2010), (Yang et al., 2015)
Metabolites			
RSV-3-O-sulfate		ATR/p53	(Aires et al., 2013)
RSV-3-O-glucuronide		ATR/p53	(Aires et al., 2013)
RSV-4'-O-glucuronide		ATR/p53	(Aires et al., 2013)
Analogs			
Pterostilbene		MAT1	(Dhar et al., 2016)
DHS		-	(Savio et al., 2016)
HPIMBD		Wnt	(Anwesha Chatterjee, 2015)